DEPARTMENT OF HEALTH AND HUMAN SERVICES

Centers for Disease Control and Prevention

[Docket No. CDC-2021-0053]

The Systematic Review Report for Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS); Notice of Availability

AGENCY: Centers for Disease Control and Prevention (CDC), Department of Health and Human Services (HHS).

ACTION: Notice.

SUMMARY: The Centers for Disease Control and Prevention (CDC), located within the Department of Health and Human Services (HHS), announces the availability of the final systematic review report titled "Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)." The report is accompanied by a summary of public comments.

DATES: The final document is available [INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: The document may be found in the docket at www.regulations.gov, Docket No. CDC-2021-0053 in the Supporting Materials tab and at https://www.cdc.gov/me-cfs/programs/evidence-review.html.

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SUPPLEMENTARY INFORMATION: In 2022, the systematic review titled "Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)" conducted by the Pacific Northwest Evidence-Based Practice Center at Oregon Health and Science University, concluded that there is limited evidence on effective treatments for ME/CFS. The review updates a 2014 Agency for Healthcare Research and Quality (AHRQ)-funded review and its 2016 addendum. It also expands upon the prior AHRQ review by including children as well as adults, evaluating harms as well as benefits of diagnosis, and evaluating effects of treatment on depression, anxiety, sleep quality, pain, and other symptoms associated with ME/CFS in addition to fatigue, function, and quality of life. The report evaluates the quality of the scientific literature and does not make recommendations or guidelines. While improving clinical care remains a critical issue, the lack of sufficient evidence from the review resulted in the decision for CDC not to proceed with developing clinical management guidelines.

On May 17, 2021, CDC published a notice in the *Federal Register* (87 FR 26733) requesting public comment on the draft report of the systematic review for ME/CFS. One

hundred and thirty-five commenters provided feedback including those from academia, professional organizations, advocacy groups, and the public. Some of the comments received were from organizations that represented patient advocacy groups. CDC highly values insights gained from these public comments and especially thanks patients living with ME/CFS, who shared their personal experiences in this public forum.

Comments were centered around several themes. All comments were carefully reviewed and considered by CDC. Themes from the comments included (1) concerns with cognitive behavioral therapy and graded exercise therapy; (2) personal testimonials; (3) inclusion of studies with high risk of bias; (4) exclusion of certain studies on harms evidence; (5) concerns with case definitions and impact on the systematic review; (6) interpretation of results; (7) CDC programmatic concerns and recommendations; and (8) recommended references.

Comments: *Concerns with cognitive behavioral therapy (CBT) and graded exercise therapy (GET):* Commenters expressed concern with inclusion of the CBT and GET in the systematic review, including personal testimony of harms experienced after attempting treatment with CBT or GET, and critiques of the proposed mechanism (or lack of) of CBT or GET.

Response: CDC acknowledges the concerns that commenters have about the inclusion of CBT and GET in this systematic review. The authors of this systematic review report were aware of the criticisms of CBT and GET as treatments for ME/CFS. The studies for CBT and GET were included in the report because they met the inclusion and exclusion criteria of this systematic review protocol, and the limitations of the evidence on these therapies were described in the report as well. The purpose of this systematic review was to provide a summary of available published literature, including limitations. This systematic review does not make treatment recommendations, and therefore, does not recommend GET or CBT.

Comments: *Personal testimonials:* These testimonials spoke to the sincere frustration and desperation experienced by many patients with ME/CFS, including difficulty finding providers familiar with ME/CFS, struggles during and after attempted treatment with GET or CBT, and the impact of ME/CFS on their daily lives.

Response: CDC appreciates the patients living with ME/CFS to share their stories and acknowledges the struggles that they face on a daily basis. CDC highly values insights gained from these public comments. Some patients felt that this systematic review was recommending treatment with GET or CBT. However, the purpose of this

systematic review was to provide a summary of available published literature, including limitations. This systematic review does not make treatment recommendations, and therefore, does not recommend GET or CBT.

Comments: *Inclusion of studies with high risk of bias:* Commenters expressing concern that unblinded trials and studies reporting participant-reported outcomes should have been rated high risk of bias or should be downgraded unless there were other methodological limitations.

Response: CDC recognizes commenters' concerns about such studies. For interventions where blinding is not possible, we followed the standard approach used in many other systematic evidence reviews and downgraded for open-label design, but did not necessarily downgrade to high risk of bias unless there were other methodological limitations.

Comments: *Exclusion of certain studies on harms evidence:* Commenters suggest that the review missed potentially relevant evidence on harms by excluding observational studies and patient surveys.

Response: CDC understands commenters' concern about exclusion of these studies. We will take them into consideration for future systematic reviews. This review focused on randomized controlled trials (RCT) for

evaluation of benefits and harms of treatments because observational studies and non-RCTs are susceptible to bias and confounding, particularly for more subjective outcomes like those evaluated in this report.

Comments: *Concerns with case definitions and impact on the systematic review:* Some commenters suggested the removal of studies that used older case definitions for the inclusion of this review.

Response: CDC respects the reasons for commenters' concerns with the case definitions used in the report, as many case definitions have emerged over the past several decades. To address the issue of the multitude of case definitions, regrouped analyses were performed for various case definitions.

Comments: *Interpretation of results:* Commenters questioned the use and interpretation of meta-analysis in the systematic review, due to high heterogeneity, low strength of evidence, and high risk of bias studies.

Response: CDC appreciates commenters' concerns with meta-analysis methodology. In the revision we incorporated some of these comments and added more details to address these concerns. Essentially, the meta-analysis results were restructured for visualization and to facilitate the

interpretation of results, thus overcoming this challenge and allowing for useful information to be reviewed.

Comments: *CDC programmatic concerns and recommendations*: Commenters included requests or recommendations to the CDC ME/CFS program regarding future research and/or guidelines.

Response: CDC appreciates the comments for improving the CDC ME/CFS program and will address them with leadership during program planning activities.

Comments: *Recommended references:* Commenters suggested additional information available on websites and in scientific publications.

Response: CDC recognizes the importance of reviewing these suggested references. Each suggested reference was assessed for this current review with pre-established inclusion/exclusion criteria. For future systematic reviews CDC may consider different criteria, which may allow for taking the suggested references into further consideration.

Based on public comments, CDC revised the final report to include (1) information about the decision not to proceed with developing clinical management guidelines; (2) regrouping of plots for the meta-analysis by case definition to facilitate the interpretation of results by various case definitions; (3) regrouping limitations into

two major categories (study and clinical trial limitations and limitation in methods used to conduct the review); and (4) adding a description about the importance of collecting common data elements via standardized instruments or other assessment tools. The final report and a thematic summary of responses to public comments can be found in the Supporting Materials tab of the docket and at https://www.cdc.gov/me-cfs/programs/evidence-review.html.

Although ultimately, at this time, CDC did not find sufficient evidence from the review to proceed with the development of clinical management guidelines for ME/CFS, the review was instrumental in spotlighting the research gaps in the currently available literature, and consequently, possible improvements for future clinical trial design and ways to leverage funding resources for clinical trials.

Dated: January 11, 2023.

Tiffany Brown,

Acting Executive Secretary,

Centers for Disease Control and Prevention.

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